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(21) International Application Number: PCT/US97/16348 (22) International Filing Date: 19 September 1997 (19.09.97) (30) Priority Data: 60/026,848 27 September 1996 (27.09.96) US (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WARPELIOSKI, Martha, A. [US/US]; 7600 Curry Lane, Portage, MI 49024 (US). HARPER, Donald, E. [US/US]; 11520 Channel Drive, Plainwell, MI 49080 (US). (74) Agent: YANG, Lucy, X.; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: β -SULFONYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASES INHIBITORS <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div> (57) Abstract <p>The present invention provides a compound of formula (I), or pharmaceutical acceptable salts thereof wherein R₁ is C₄₋₁₂ alkyl, C₄₋₁₂ alkenyl, C₄₋₁₂ alkynyl, -(CH₂)_n-C₃₋₈ cycloalkyl, -(CH₂)_n-aryl or -(CH₂)_n-het; R₂ is C₁₋₁₂ alkyl, C₂₋₁₂ alkenyl, C₂₋₁₂ alkynyl, -(CH₂)_n-C₃₋₈ cycloalkyl, -(CH₂)_n-C₃₋₈ cycloalkenyl, -(CH₂)_n-aryl, -(CH₂)_n-het, -(CH₂)_n-Q, -(CH₂)_n-X-R₄ or -(CH₂)_n-CHR₅R₆. The compounds are inhibitors of matrix metalloproteinases involved in tissue degradation.</p>		

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**β -SULFONYL HYDROXAMIC ACIDS
AS MATRIX METALLOPROTEINASES INHIBITORS**

FIELD OF THE INVENTION

5 The present invention relates to novel β -sulfonyl hydroxamic acids, to pharmaceutical compositions containing them, and to the method of using them. The compounds of the invention are inhibitors of matrix metalloproteinases involved in tissue degradation.

10 BACKGROUND OF THE INVENTION

Loss of connective tissue integrity occurs in many disease processes, including osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, asthma and other diseases related to connective tissue degradation. Although there is a high incidence of these diseases in the developed world, there is no treatment that prevents the tissue damage that occurs. Considerable lines of scientific evidence indicate that uncontrolled connective matrix metalloproteinase (MMPs) activity is responsible for the damage, and as a consequence the inhibition of these enzymes has become the target for therapeutic intervention (see Matrisian, L. M., *Bases*, Vol. 14, pp 445-463 (1992); Emonard, H. et al., *Cellular and molecular Biology*, Vol. 36, pp 131-153 (1990); Docherty, A. J. P. et al., *Annals of the Rheumatic*, Vol. 49, pp 469-479 (1990)).

Hydroxamic acid derivatives are a class of known therapeutically active MMPs inhibitors and there are numerous references in the art disclosing a variety of hydroxamic acid derivatives. For example, European Patent Publication 0,606,046 A1 discloses arylsulfonamido-substituted hydroxamic acids useful as matrix metalloproteinase inhibitors. International Publication Nos. WO 95/35275 and WO 95/35276 disclose sulfonamide hydroxamic acid and carboxylic acid derivatives useful as matrix metalloproteinases inhibitors. All these references relate to sulfonamide hydroxamic acids. The compounds of this invention are novel and distinct from all other sulfonamide hydroxamic acids in that the usual nitrogen atom is replaced by a carbon atom. The invention provides sulfonyl hydroxamic acid derivatives.

35 The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and

hence are useful for the treatment of matrix metallo endoproteinase diseases such as osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, inflammation, asthma, and other diseases related to connective tissue degradation.

5

INFORMATION DISCLOSURE

The following references disclose sulfonyl hydroxamic acid derivatives.

International Publication No. WO 95/09841 discloses hydroxamic acid compounds useful as inhibitors TNF and matrix metalloproteinases.

10 International Publication No. WO 93/20047 discloses hydroxamic acid compounds useful as inhibitors of tumour necrosis factor production and of matrix metalloproteinases.

International Publication No. WO 90/05719 discloses hydroxamic acid compounds useful in the management of diseases involving tissue degradation
15 and/or the promotion of wound healing.

The hydroxamic acid compounds in the above identified references have an obligatory peptide backbone. The compounds of the present invention are distinct from the above noted references in that they do not have a peptide backbone.

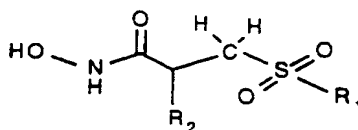
The European Patent Application EP 0780 386 A1 discloses matrix
20 metalloproteinases inhibitors useful in the treatment of mammals having disease states alleviated by the inhibition of such matrix metalloproteinases.

International Publication No. WO 97/24117 discloses substituted aryl, heteroaryl, arylmethyl or heteroarylmethyl hydroxamic acid compounds especially useful for inhibiting the production or physiological effects of TNF in the treatment
25 of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF).

SUMMARY OF THE INVENTION

The present invention provides novel compounds of formula I

30



35

I

or pharmaceutical acceptable salts thereof wherein:

R₁ is

- a) C₄₋₁₂ alkyl,
- b) C₄₋₁₂ alkenyl,
- 5 c) C₄₋₁₂ alkynyl,
- d) -(CH₂)_h-C₃₋₈ cycloalkyl,
- e) -(CH₂)_h-aryl,
- f) -(CH₂)_h-aryl substituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, halo, -NO₂, -CF₃, -CN, or -N(C₁₋₄ alkyl)₂,
- 10 g) -(CH₂)_h-het, or
- h) -(CH₂)_h-het substituted with C₁₋₄ alkyl, or halo;

R₂ is

- a) C₁₋₁₂ alkyl,
- b) C₁₋₁₂ alkyl substituted with one to three halo, -CN, -NO₂, -CF₃,
15 -N(R₃)₂, -SR₃, or OH,
- c) C₂₋₁₂ alkenyl,
- d) C₂₋₁₂ alkenyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- e) C₂₋₁₂ alkynyl,
- f) C₂₋₁₂ alkynyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- 20 g) -(CH₂)_h-C₃₋₈ cycloalkyl,
- h) -(CH₂)_h-C₃₋₈ cycloalkyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo,
- i) -(CH₂)_h-C₃₋₈ cycloalkenyl,
- j) -(CH₂)_h-C₃₋₈ cycloalkenyl substituted with one to three C₁₋₄ alkyl,
25 C₁₋₄ alkoxy, or halo,
- k) -(CH₂)_h-aryl,
- l) -(CH₂)_h-aryl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, -CF₃, -OH, -NO₂, -CN, -N(R₃)₂, -SR₃, -SO₂(C₁₋₄ alkoxy), -C(=O)R₃, or -NC(=O)R₃,
- 30 m) -(CH₂)_h-aryl substituted with one to five halo,
- n) -(CH₂)_h-het,
- o) -(CH₂)_h-het substituted with one to two C₁₋₄ alkyl, or halo,
- p) -(CH₂)_h-Q,
- q) -(CH₂)_h-Q substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, halo,
35 or phenyl,
- r) -(CH₂)_i-X-R₄, optionally the -(CH₂)_i- chain can be substituted with

C_{1-4} alkyl or phenyl, which in turn can be substituted with one to three halo or C_{1-4} alkyl, or

s) $-(CH_2)_iCHR_5R_6$;

R_3 is

5

- a) H,
- b) C_{1-4} alkyl,
- c) $-(CH_2)_h$ -phenyl, or
- d) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo;

10 X is

- a) -O-,
- b) $-S(=O)_j-$,
- c) $-NR_7-$,
- d) $-S(=O)_2NR_8-$, or

15

e) $-C(=O)-$;

R_4 is

- a) H,
- b) C_{1-4} alkyl,
- c) $-(CH_2)_h$ -phenyl,
- d) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, $-NO_2$, or $-CN$, or
- e) $-(CH_2)_h$ -het;

20

R_5 is

- a) C_{1-4} alkyl, or
- b) $-C(=O)R_3$;

25

R_6 is

- a) $-C(=O)R_3$, or
- b) $-(CH_2)_hC(=O)R_3$;

R_7 is

30

- a) H,
- b) C_{1-4} alkyl,
- c) $-(CH_2)_h$ -phenyl,
- d) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo,

35

- e) $-C(=O)-R_3$,
- f) $-S(=O)_2R_3$, or

g) $-C(=O)OR_3$;

R_8 is

a) C_{1-4} alkyl,

b) $-(CH_2)_h$ -phenyl, or

5 c) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated heterocyclic moiety having one to three atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

10 Q is 5- to 10-membered saturated heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur;

h is 0, 1, 2, 3, 4, 5, or 6; i is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and j is 0, 1, or 2.

The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and
15 hence are useful for the treatment of matrix metallo endoproteinase diseases

DETAILED DESCRIPTION OF THE INVENTION

For the purpose of the present invention, the carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum
20 and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} defines the number of carbon atoms present from the integer "i" to the integer "j", inclusive. Thus, C_{1-4} alkyl refers to alkyl of one to four carbon atoms, inclusive, or methyl, ethyl, propyl, butyl and isomeric forms thereof.

The terms " C_{1-4} alkyl", " C_{4-8} alkyl", " C_{1-12} alkyl", and " C_{1-18} alkyl" refer to
25 an alkyl group having one to four, four to eight, one to twelve, or one to eighteen carbon atoms respectively such as; for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and their isomeric forms thereof, preferably an alkyl group of R_1 having four to eight carbon atoms, and an alkyl group of R_2 having one to eight carbon atoms.

30 The terms " C_{2-12} alkenyl" and " C_{4-8} alkenyl" refer to at least one double bond alkenyl group having two to twelve carbon atoms respectively such as; for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, heptdienyl, octenyl, octadienyl, octatrienyl, nonenyl, undecenyl, dodecenyl, and their isomeric forms thereof, preferably an alkenyl group of R_1 having four to eight carbon atoms,
35 and an alkenyl group of R_2 having two to eight carbon atoms.

The term " C_{2-12} alkynyl" refers to at least one triple bond alkynyl group

having two to twelve carbon atoms such as; for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, octadiynyl, octatriynyl, nonynyl, nonediynyl, and their isomeric forms thereof, preferably an alkynyl group of R_1 having four to eight carbon atoms, and an alkenyl group of R_2 having two to eight carbon atoms.

5 The term " C_{3-8} cycloalkyl" refers to a cycloalkyl having three to eight carbon atoms such as; for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and their isomeric forms thereof, preferably an cycloalkyl group having three to six carbon atoms.

10 The term " C_{3-8} cycloalkenyl" refers to a cycloalkenyl having three to eight carbon atoms such as; for example, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and their isomeric forms thereof, preferably an cycloalkyl group having five to six carbon atoms.

15 The terms " C_{1-4} alkoxy", " C_{1-6} alkoxy", and " C_{1-8} alkoxy" refer to an alkyl group having one to four, one to six, or one to eight carbon atoms respectively attached to an oxygen atom of hydroxyl group such as; for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy, heptyloxy, or octyloxy and their isomeric forms thereof.

20 The term "aryl" refers to monocarbocyclic or bicarbocyclic aromatic moiety such as; for example phenyl, naphthyl, biphenyl. Each of these moieties may be substituted as appropriate. Aryl is preferably phenyl or phenyl substituted with C_{1-4} alkyl, C_{1-4} alkoxy, fluoro, chloro, bromo, $-NO_2$, $-CF_3$, $-N(C_{1-4} \text{ alkyl})_2$, $-C(=O)R_3$, or $-NC(=O)R_3$.

25 The term "het" refers to a 5- to 10-membered unsaturated heterocyclic moiety having one or more atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as; for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 2-quinolyl, 3-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinoxaliny, 1-phthalazinyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-indolyl, 3-indolyl, 3-indazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzimidazolyl, 2-benzofuranyl, 3-benzofuranyl, benzoisothiazole, benzoisoxazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1-indolyl, 1-indazolyl, 2-isindolyl, 1-purinyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, preferably pyridyl, quionlinyl, pyrrolyl, thienyl, thiazolyl, or indolyl.
35 Each of these moieties may be substituted with one to two C_{1-4} alkyl, $-NO_2$, fluoro,

chloro, or bromo as appropriate.

The term "Q" refers to a 5- to 10-membered saturated heterocyclic moiety having one to two atoms selected from the group consisting of oxygen, nitrogen, and sulfur such as; for example, piperidinyl, 2-, 3-, or 4-piperidinyl, [1,4]piperazinyl, morpholinyl, 2- or 3-morpholinyl, thiomorpholinyl, dioxolanyl, imidazolidinyl, [1,3]oxathiolanyl, [1,3]oxazolidinyl, pyrrolidinyl, butyrolactonyl, butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, pyrazolidinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, isoxazolidinyl, 3-oxo-isoxazolidinyl, [1,3]-thiazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl, preferably butyrolactamyl, succinimidyl, glutarimidyl, valerolactamyl, 2,5-dioxo-[1,4]-piperazinyl, 3-oxopyrazolidinyl, 2-oxo-imidazolidinyl, 2,4-dioxo-imidazolidinyl, 2-oxo-[1,3]-oxazolidinyl, 2,5-dioxo-[1,3]-oxazolidinyl, 3-oxo-isoxazolidinyl, 2- or 4-oxo-[1,3]-thiazolidinyl.

The term halo refers to fluoro, chloro, bromo, or iodo, preferably fluoro, chloro, or bromo.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form. Some of the compounds of this invention may form metal salts such as sodium, potassium, calcium and magnesium salts and these are embraced by the term "pharmaceutically acceptable salts".

The compounds of formula I of this invention contain a chiral center at the α -position of hydroxamic acids, as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on the substituents, additional chiral centers and other isomeric forms may be present in any of the R_2 groups, and this invention embraces all possible stereoisomers and geometric forms in this group.

R_1 is preferably n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methylbutyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-tert-butylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl,

4-n-butyloxyphenyl, benzyl, 4-phenylbenzyl, 2-, 3-, or 4-fluorobenzyl, 2-, 3-, 4-chlorobenzyl, 2-, 3-, 4-bromobenzyl, and 4-ethoxybenzyl. More preferably R_1 is n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-butoxyphenyl, benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-bromobenzyl, and 4-ethoxybenzyl.

R_2 is preferably methyl, 1-cyano-1-phenyl methyl, 2-cyano ethyl, 2-phenylethyl, 2-bromo-2-phenylethyl, 2-bromoethyl, propyl, isopropyl, 3-chloropropyl, 3-bromopropyl, n-butyl, isobutyl, 3-methylbutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methylbutyl, n-hexyl, n-heptyl, n-octyl, n-hexadecyl, n-octadecyl, 2-propenyl, 2-propynyl, 3-butenyl, 4-pentenyl, 3-butenynyl, 4-pentenynyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-cyclohexylbutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminopropyl, phenylaminomethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-nitrophenyl, 4-ethoxyphenyl, benzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, and 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-ethoxybenzyl, 4-nitrobenzyl, methylcarbonyl, 1-methylcarbonyl methyl, 2-phenylcarbonyl ethyl, isopropylcarbonyl, methoxycarbonyl, ethoxycarbonyl, 1,1-ethoxycarbonyl methyl, 2,2-ethoxycarbonyl ethyl, 1,2-ethoxycarbonyl ethyl, 2-methoxycarbonyl propyl, 3-methoxycarbonyl propyl, 1-ethoxycarbonyl methyl, 1-ethoxycarbonyl ethyl, phenylcarbonyl, phenylcarbonyl methyl, pyridylcarbonyl methyl, pyridylmethyl, pyridylethyl, quionlinylmethyl, pyrrolyl methyl, indolyl methyl, thienyl, thiazolyl, thienylmethyl, thienylethyl, piperdiny methyl, piperazinyl methyl, morpholino methyl, morpholino ethyl, morpholino propyl, thiomorpholino methyl, thiomorpholino propyl, 4-methoxybenzenesulfonyl methyl, 3-(4-methoxybenzenesulfonyl)amino propyl, 3-(4-methoxybenzenesulfonyl)propyl, 3-hydroxy, amino, 3-phenoxy propyl, 2-phenyl ethyloxy, (4-butoxybenzenesulfonyl) methyl, methyl-3-(1,5,5-trimethylhydantoin), methyl-3-(1-butyl-5,5-dimethylhydantoin), (4-methoxybenzenesulfonyl)methyl, (4-chlorobenzenesulfonyl)-methyl, (4-bromobenzenesulfonyl)methyl, (n-butylsulfonyl)methyl, (n-octylsulfonyl)-methyl, 3-(4-methoxybenzenesulfonyl)propyl, (4-methylbenzenesulfonyl)methyl, (benzenesulfonyl)methyl, methyl-3-(1-methylhydantoin), methyl-3-(1-butylhydantoin) and methyl-3-(5,5-dimethylhydantoin). More preferably R_2 is (4-methoxybenzenesulfonyl)methyl, (4-chlorobenzenesulfonyl)-methyl,

(4-bromobenzenesulfonyl)methyl, (n-butylsulfonyl)methyl, (n-octylsulfonyl)methyl, 3-(4-methoxybenzenesulfonyl)propyl, (4-methylbenzenesulfonyl)methyl, (benzenesulfonyl)methyl, methyl-3-(1-methylhydantoin), methyl-3-(1-butylhydantoin) and methyl-3-(5,5-dimethylhydantoin).

5 Particularly preferred compounds of this invention are as follows:

- (1) N-hydroxy 2-[(4-methoxybenzenesulfonyl) methyl]-3-phenyl-propionamide,
- (2) N-hydroxy 2-[(benzenesulfonyl)methyl]-3-phenyl-propionamide,
- (3) N-hydroxy 2-[(benzenesulfonyl)methyl]-propionamide,
- (4) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-
10 methoxybenzenesulfonyl)-propionamide,
- (5) N-hydroxy-2-[(4-chlorobenzenesulfonyl)methyl]-3-(4-chlorobenzenesulfonyl)-
propionamide,
- (6) N-hydroxy-2-[(4-bromobenzenesulfonyl)methyl]-3-(4-bromobenzenesulfonyl)-
propionamide,
- 15 (7) N-hydroxy-2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionamide,
- (8) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(n-octylsulfonyl)-propionamide,
- (9) N-hydroxy-2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-
propionamide,
- (10) N-hydroxy-2-[(benzenesulfonyl)methyl]-3-(benzenesulfonyl)-propionamide,
- 20 (11) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-
methoxybenzenesulfonyl)-pentanamide,
- (12) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-
propionamide,
- (13) N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-
25 propionamide,
- (14) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-
propionamide,
- (15) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-
propionamide,
- 30 (16) N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzene-
sulfonyl)-propionamide,
- (17) (+)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-
propionamide,
- (18) (-)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-
35 propionamide,
- (19) (+)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-

methoxybenzenesulfonyl)-propionamide

- (20) (-)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (21) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- (22) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- (23) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (24) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (25) (+)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide, or
- (26) (-)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

The compounds of this invention can be prepared in accordance to the process discussed below.

In Scheme I, R_1 and R_2 are the groups as defined previously. Substituted malonate esters **2** are either obtained commercially, or can be readily prepared from structure **1** by methods well known to those skilled in the art. For example, reaction of an enolate of structure **1**, generated by an appropriate base in an appropriate solvent, with an alkylating agent R_2-I (I is bromo, chloro, tosylate, mesylate, epoxides, etc.) provides the desired substituted malonate esters **2**. See: *Organic Synthesis*, Vol. 1 p 250 (1954); *Organic Synthesis*, Vol. 3, p 495 (1955). Compound **2** is hydrolyzed to mono-acid compound **3** by reaction with one equivalent of an appropriate base such as alkali hydroxide in an appropriate solvent at a temperature ranging from 0°C to 30°C . In the presence of formaldehyde and piperidine in an appropriate solvent such as pyridine, ethanol, dioxane at refluxing temperatures, compound **3** is converted to acrylic esters **4**. In many cases, acrylic esters **4** are commercially available. A thiol (H-SR_1) is added to the acrylic ester **4** at room temperature to afford sulfide esters **5** in the presence of either a catalytic amount of alkoxide in alcoholic solvent or a tertiary amine base in chloroform. The resultant sulfides **5** are readily oxidized to sulfones **6** by an oxidizing agent such as meta-chloroperoxybenzoic acid (MCPBA) in an appropriate solvent such as methylene chloride, or using hydrogen peroxide in acetic acid as a solvent. The esters can be hydrolyzed by procedures well known in the art such as using 6N HCl and refluxing

for 10 to 20 hours or using iodotrimethylsilane in chloroform to afford free acids 7. Coupling of acids 7 with hydroxylamine hydrochlorides to form hydroxamates 9 may be achieved by several routes well known to those skilled in the art. For example, acids 7 can be activated by chloroethylformate in dry THF or a similar compatible solvent, or by a carbodiimide condensing agent such as EDC, with or without HOBT, in DMF and methylene chloride. A tertiary amine is required in both situations. The subsequent reaction of activated 7 with hydroxylamine provides the desired hydroxamic acid derivatives. Alternatively, acids 7 may be condensed, using the same reagents as described above, with benzyl-protected hydroxylamine hydrochloride, to produce the protected hydroxamates 8. Compounds 8 are often easier to purify, and may readily be hydrogenolytically cleaved to the free hydroxamates 9 by a palladium catalyst in alcoholic solvents. Other protected hydroxylamines such as tert-butyl hydroxylamine may also be used, and the free hydroxamate can be obtained by treating it with trifluoroacetic acid.

A second method of preparing the compounds of the invention is to utilize commercially available acrylic acids 10 as shown in Scheme II. Treatment of acrylic acids with thiols affords compounds 11. The reaction may be accomplished in refluxing an appropriate solvent such as dioxane with piperidine as a catalyst. See: *Annalen*, Vol. 564, pp 73-78 (1949). A variation of this method is shown in Scheme III in which α -bromomethyl acrylic acids 12 are reacted with two moles of thiols to afford bis-sulfides 13. Oxidation of the resulting sulfides with meta-chloroperbenzoic acid or with excess hydrogen peroxide provides compound 7 in Scheme II and compound 14 in Scheme III, respectively. The remaining synthetic steps which lead to products 9 and 15 are similar to the procedures outlined in Scheme I.

Schemes IV, V and VI depict methods especially adapted to the preparation of the compounds of formula I wherein the R_2 group contains heteroatoms. In Scheme IV, substituent R_4 is defined as previously. Group I in structure 16 is bromo, chloro, tosylate, mesylate, or epoxides, and may be replaced by an agent R_4 -X-H according to procedures well known in the art (X may be O, NR_7 , S and etc.). The remaining synthetic steps which lead to compound 18 are similar to the procedures outline in Scheme I.

In Scheme V a suitably protected cysteine (P in structure 19 is a protecting group) can be converted to the corresponding thiol 20. After removing the protecting group, a R_7 group (as defined previously) can be introduced into the nitrogen atom

as shown in structure 23. The procedure outlined in Scheme V is discussed in further detail in Synthesis Communication, Vol. 16, No. 5, p. 565 (1986). This method can be carried out for both the racemate or a single enantiomer. Following the general procedures as described above but starting with enantiomerically enriched isomers, the desired single enantiomer, either *R* or *S* can be obtained.

In Scheme VI, structure 12 is first reacted with one equivalent of thiol or sulfinate in a suitable solvent such as toluene in the absence or presence of a suitable base such as sodium bicarbonate or triethyl amine, at ambient temperature or reflux, to afford 25 or 26, respectively. Conversion of 25 to 26 is accomplished with an oxidant such as meta-chloroperbenzoic acid, in a suitable solvent such as methylene chloride at 0° C. Intermediate 26 is reacted with the anion or conjugate acid of W (wherein W is a group attached via a heteroatom such as oxygen, nitrogen or sulfur) in a solvent such as toluene or dimethylformamide, in the absence or presence of a basic catalyst such as sodium bicarbonate or triethyl amine, preferably at reflux to provide intermediate 7, in which the R₂ group may be -CH₂XR₄, -CH₂-het, or -CH₂-Q. The remaining synthetic steps which lead to final hydroxamic products 9 are similar to the procedures outlined in Scheme I.

In addition to Schemes IV, V and VI, the compounds of formula I wherein the R₂ group contains heteroatoms may also be prepared according to Scheme II by using structure 12. In this method, α-bromomethyl acrylic acid 12 is reacted with one equivalent of anion or conjugate acid of W to provide acrylic acids 10, in which the R₂ group may be -CH₂-W (wherein W is as defined above). The remaining synthetic steps which lead to final hydroxamic products 9 are similar to the procedures outlined in Scheme II. When W is a thiol or thiolate, the sulfur contained in R₂ may be oxidized to a sulfoxide or sulfone, give rise to, for example, unsymmetrical bis-sulfonyl hydroxamates.

The chemistry in Schemes I, II, IV and VI proceeds through achiral or racemic intermediates and pure enantiomers of the final products may be obtained by resolution of intermediates 5-9 or 11 by chiral chromatography or classical derivatization methods such as chiral salt formation of intermediate 7.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of formula I of this invention with a solid or liquid pharmaceutically acceptable carrier, and optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules and suppositories. A solid carrier can be at least one substance which may

also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water, water-propylene glycol, and water-polyethylene glycol systems, optionally containing conventional coloring agents, flavoring agents, stabilizers and thickening agents.

10 The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula I according to this invention.

15 The quantity of active component, that is the compounds of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

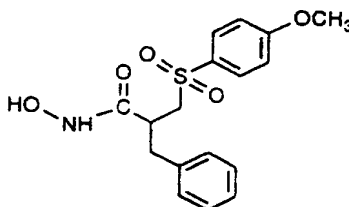
20 In therapeutic use for treating a patient, suffering from or susceptible to diseases involving connective tissue degradation, or inhibiting various enzymes from the matrix metalloproteinase family, including collagenase, stromelysin, and gelatinase, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the patient undergoing treatment which will be effective to inhibit such enzymes. Generally, an effective amount of the active compound will be in the range of about 0.1 to about 100 mg/kg. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of connective tissue degradation being treated, and the particular compounds being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of the present invention inhibit various enzymes from the matrix metalloproteinase family, predominantly stromelysin and gelatinase, and hence are useful for the treatment of matrix metallo endoproteinase diseases such as osteoarthritis, rheumatoid arthritis, septic arthritis, osteopenias such as
5 osteoporosis, tumor metastasis (invasion and growth), periodontitis, gingivitis, corneal ulceration, dermal ulceration, gastric ulceration, and other diseases related to connective tissue degradation. Such diseases and conditions are well known and readily diagnosed by physician of ordinary skill.

Pharmaceutical compositions for parenteral administration will generally
10 contain a pharmaceutically acceptable amount of the compounds according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as; for example, water-for-injection and a suitably buffered isotonic solution having a pH of about 3.5-6. Suitable buffering agents include; for example, trisodium orthophosphate, sodium
15 bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine, to name a few. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml. The resulting liquid pharmaceutical composition will be administered so as to obtain the
20 above-mentioned inhibitory effective amount of dosage. The compounds of formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an
25 illustration of and not a limitation upon the scope of the invention.

EXAMPLE 1 Preparation of N-hydroxy 2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionamide.



Step 1 Preparation of benzylmalonic acid monoethyl ester.

Benzylmalonic acid diethyl ester (10 g, 40 mmol) in 25 mL of ethanol is cooled to 0° C. Potassium hydroxide (2.5 g, 40 mmol) dissolved in 25 mL of ethanol is added dropwise over 50 minutes. The cooling bath is removed and the mixture is stirred for one additional hour. The volume of solvent is reduced by evaporation *in vacuo*, and the residual solution is poured into aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The aqueous phase is acidified with aqueous 10% HCl and extracted twice with ethyl acetate. The organic phase is dried with a brine extraction, filtered from anhydrous sodium sulfate, and concentrated *in vacuo*, yielding 8.08 g of the title compound as a colorless oil.

Step 2 Preparation of 2-benzyl-2-propenoic acid ethyl ester.

Benzylmalonic acid monoethyl ester (8.0 g, 36 mmol), 7 mL of pyridine, 0.36 mL (3.6 mmol) of piperidine, and 1.06 g (35 mmol) of paraformaldehyde is refluxed under nitrogen for 1.5 hours in an oil bath maintained at 130° C. After cooling for 0.5 hours the mixture is partitioned between 100 mL of water and 100 mL of hexane. The aqueous phase is re-extracted with 50 mL of hexane. The organic phase is washed with aqueous 10% HCl, water, 1 M sodium bicarbonate, and brine. It is dried over anhydrous sodium sulfate and concentrated *in vacuo*, yielding 5.8 g of the title compound as a colorless oil.

Step 3 Preparation of 2-[(4-methoxybenzenethio)methyl]-3-phenyl-propenoic acid ethyl ester.

4-Methoxybenzenethiol (0.6 mL, 4.7 mmol) in 1 mL of ethanol is cooled in an ice bath with stirring. Ethanolic sodium ethoxide solution 0.13 mL (0.34 mmol) is added. After 15 minutes 1.0 g (5.3 mmol) of 2-benzyl-2-propenoic acid ethyl ester in 1 mL of ethanol is added dropwise over about 2 minutes. The ice bath is removed and the reaction mixture is allowed to stir for 17 hours. The mixture is evaporated *in vacuo* and partitioned between ethyl acetate and aqueous 5% HCl. The organic phase is concentrated and chromatographed over silica gel, eluting with hexane:acetone (98:2), to afford 1.04 g of the title compound as a colorless oil.

Step 4 Preparation of 2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionic acid ethyl ester.

To a solution of 2-[(4-methoxybenzenethio)methyl]-3-phenyl-propionic acid ethyl ester (1.51 g, 4.6 mmol) in 50 mL of methylene chloride, cooled in an ice bath, is added 2.17 g (10 mmol) of solid MCPBA portion wise over 5 minutes. The cooling bath is removed, and the mixture is stirred at room temperature overnight. The suspension is filtered and the solids washed with methylene chloride. The organic

solution is extracted with three portions of 1M sodium bicarbonate, dried by extraction with brine, filtered from anhydrous sodium sulfate, and concentrated. Chromatography on silica gel, eluting with methylene chloride:acetone (99:1), afforded 1.31 g of the title compound as a colorless oil.

- 5 Step 5 Preparation of 2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionic acid.

A mixture of 0.56 g (1.5 mmol) of 2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propanoic acid ethyl ester and 8 ml of 6N HCl is heated at 115 °C for 17 hours. The mixture is transferred to 100 ml of ice-water and extracted with two
10 portions of ethyl acetate. The organic phase is extracted with three 50 mL portions of aqueous 5% sodium bicarbonate. The bicarbonate solution is poured over ice and acidified with concentrated HCl. The acidified aqueous mixture is extracted with three 50 mL portions of ethyl acetate and the combined organic extracts are concentrated *in vacuo* to yield 0.45 g of the title compound as a white solid.

- 15 Step 6 Preparation of N-benzyloxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionamide.

A solution of 2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionic acid (1.05 g, 3.14 mmol) and 0.69 mL (6.3 mmol) of NMM in dry THF, under nitrogen, is cooled in an ice bath. Ethyl chloroformate (0.33 mL, 3.5 mmol) in 7 mL of THF is
20 added dropwise over 5 minutes. The suspension is stirred at 0° C for 10 minutes, after which a slurry of O-benzylhydroxylamine hydrochloride (0.64 g, 4 mmol) and NMM (0.44 mL, 4 mmol) in 7 mL of THF is introduced in several portions. The mixture is stirred for 10 minutes and stored at 10° C overnight. The mixture is allowed to warm to room temperature for 0.5 hours, and is then partitioned between
25 ethyl acetate and aqueous 10% HCl. The organic phase is washed with water, three portions of 1 M sodium bicarbonate and brine. It is dried over anhydrous sodium sulfate, concentrated and chromatographed on silica gel, eluting with 40% - 50% ethyl acetate in hexanes. This affords 1.26 g of the title compound as a colorless oil.

- 30 Step 7 Preparation of N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionamide.

N-benzyloxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-phenyl-propionamide (1.25 g, 2.85 mmol) is dissolved in 45 mL of ethanol. To this is added 0.36 g of palladium hydroxide on carbon (Pearlman's catalyst), and the suspension is placed in a shaker under 15 psi of hydrogen for 2.25 hours. The catalyst is filtered off,
35 washing with ethanol, and the ethanol solution is concentrated *in vacuo* to afford, after evaporation from methylene chloride, 0.875 g of the title compound as a white

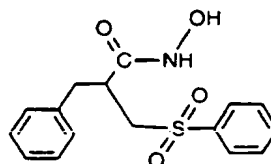
solid.

^1H NMR (DMSO) δ 10.6, 8.8, 7.67, 7.17-7.22, 7.03-7.1, 3.85, 3.55, 3.02, 2.76-2.79, 2.62; ^{13}C NMR (DMSO) δ 168.7, 164.1, 138.5, 131.3, 130.7, 129.7, 129.1, 127.3, 115.4, 56.5, 56.5, 38.3, 37.3;

5 MS (EI) m/z 349, 317, 288, 214, 171, 155, 145, 117, 107, 91.

EXAMPLE 2 Preparation of N-hydroxy 2-[(benzenesulfonyl)methyl]-3-phenyl-propionamide.

10



15

Following the general procedure outlined in EXAMPLE 1 (steps 3 to 7) and making non-critical variations but starting with thiophenol in step 3, the title compound is obtained as a white solid.

^1H NMR (DMSO) δ 10.6, 8.8, 7.73, 7.58, 7.17, 7.02, 3.60, 3.07, 2.81-2.7, 2.65-2.60;

20 ^{13}C NMR (DMSO) δ 168.2, 139.4, 138.1, 134.3, 129.9, 129.3, 128.8, 128.0, 126.9, 60.2, 55.8, 38.4;

IR (mull) cm^{-1} 3346, 2925, 1633, 1525, 1450, 1284, 1139;

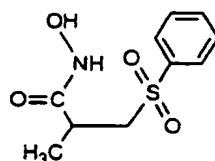
MS (EI) m/z 319, 287, 184, 164, 145, 125, 117, 91.

Calculated for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S}$: C, 60.17; H, 5.36; N, 4.39; S, 10.04; Found: C, 60.04;

25 H, 5.46; N, 4.28; S, 9.88.

EXAMPLE 3 Preparation of N-hydroxy 2-[(benzenesulfonyl)methyl]-propionamide.

30



35 Step 1 Preparation of 2-[(benzenesulfonyl)methyl]-propiononic acid

To 1 mmol of 2-[(benzenethio)methyl]-propionic acid in 10 mL of methylene

chloride cooled in an ice bath is added 0.5 g (2.3 mmol) of solid MCPBA in several portions. The reaction mixture is stirred at room temperature for 6 hours, and refrigerated overnight. The suspension is filtered, and the filtrate is concentrated and chromatographed on silica gel, eluting with 25% ethyl acetate and 0.5% acetic acid in hexanes, followed by 50% ethyl acetate, 0.5 % acetic acid, in hexanes. Evaporation of the solvents left 0.225 g of the title compound as a white solid.

Step 2 Preparation of N-hydroxy 2-[(benzenesulfonyl)methyl]-propionamide.

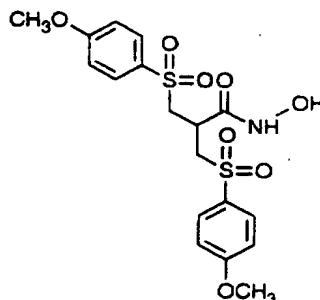
Following the general procedure outlined in EXAMPLE 1 (steps 6-7) and making non-critical variations but starting with 2-[(benzenesulfonyl)methyl]-propionic acid in step 6, the title compound is obtained as a white solid.

^1H NMR (DMSO) δ 10.6, 8.8, 7.87, 7.74, 7.64, 3.53, 3.27, 2.58, 1.05;

^{13}C NMR (DMSO) δ 170.0, 139.8, 134.4, 129.9, 128.0, 57.6, 32.3, 19.0;

MS (EI) m/z 243, 211, 141, 125, 77.

EXAMPLE 4 Preparation of N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide



Step 1 Preparation of 2-(4-methoxybenzenethiomethyl)-3-(4-methoxybenzenethio)-propionic acid.

To a stirred mixture of 2-bromomethylacrylic acid (10 g, 60 mmol) in 125 mL of toluene at room temperature, is added sodium bicarbonate (15 g, 180 mmol) and 4-methoxybenzenethiol (16.5 mL, 140 mmol) and this mixture is refluxed overnight. The mixture is partitioned between aqueous sodium bicarbonate and ethyl acetate, the aqueous phase is acidified to pH 2 with concentrated hydrochloric acid, and extracted with ethyl acetate. The combined organic extracts are concentrated *in vacuo* to afford the title compound as white solid.

^1H NMR (DMSO) δ 12.1, 7.25, 6.85, 3.74, 3.05, 2.50;

^{13}C NMR (DMSO) δ 174.60, 159.59, 134.05, 125.57, 115.66, 55.93, 55.63, 45.38,

36.93.

Step 2 Preparation of 2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionic acid.

A stirred mixture of 2-(4-methoxybenzenethiomethyl)-3-(4-methoxybenzenethio)-propionic acid (18.5 g, 5 mmol) in methylene chloride (250 mL) is cooled in a dry ice/acetone bath and m-chloroperoxybenzoic acid (MCPBA) (54.5 g, 213 mmol) is added in small portions over approximately 30 minutes. After stirring at ambient temperature for two days and standing for one day the mixture is filtered *in vacuo* over a plug of silica gel 60 (230-400 mesh) and the filtrand is eluted with chloroform followed by chloroform/methyl alcohol/acetic acid (89:10:1). The filtrate is concentrated and triturated with hexane to afford the title compound as a white solid.

m.p. 174-5°C;

MS (FAB) *m/z* 430, 429, 239, 171, 109, 107, 103, 89, 61;

¹H NMR (DMSO) δ 7.66, 7.12, 3.86, 3.57, 2.69;

¹³C NMR (DMSO) δ 171.57, 163.97, 130.61, 130.12, 115.13, 56.28, 55.84, 30.04.

Step 3 Preparation of N-benzyloxy-2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionamide.

A mixture of 2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionic acid (5.0 g, 12 mmol) in tetrahydrofuran (30 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.3 g, 23 mmol), benzyldihydroxylamine hydrochloride (2.3 g, 14 mmol), and distilled water (30 mL) is stirred overnight. The mixture is filtered to yield a white precipitate which is dissolved in chloroform (200 mL) and filtered. The filtrate is extracted with brine (100 mL) and the organic phase concentrated *in vacuo*, to yield N-benzyloxy-2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionamide (2.24 g, 36%). The initial filtrate from the overnight reaction is transferred to ethyl acetate and extracted with 10% hydrochloric acid, water, aqueous sodium bicarbonate, and brine, and concentrated *in vacuo* to also yield the title compound as a white solid.

m.p. 151° C (dec.).

¹H NMR (DMSO) δ 11.5, 7.70, 7.37, 7.13, 4.69, 3.86, 3.50, 2.80;

¹³C NMR (DMSO) δ 166.68, 164.31, 136.72, 130.96, 130.93, 129.65, 129.09, 115.51, 77.56, 56.65, 56.34, 55.72, 34.00.

Step 4 Preparation of N-hydroxy-2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionamide.

A suspension of N-benzyloxy-2-(4-methoxybenzenesulfonylmethyl)-3-(4-

methoxybenzenesulfonyl)-propionamide (5.0 g, 9.4 mmol), Pearlman's catalyst (0.9 g), and ethyl alcohol (50 mL) is agitated under hydrogen (20 psig) at room temperature overnight. The reaction mixture is filtered through celite and the soluble solids dissolved with methyl alcohol followed by chloroform/methyl alcohol (9:1). The combined filtrates are concentrated *in vacuo* to yield N-hydroxy-2-(4-methoxybenzenesulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionamide as a white solid.

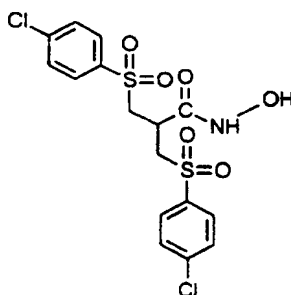
m.p. 173.5-4.5° C;

IR (mull) 3292, 1640, 1597, 1579, 1500, 1320, 1313, 1304, 1294, 1282, 1266, 1145, 1089, 1023, 838 cm⁻¹;

¹H NMR (DMSO) δ 10.9, 8.9, 7.69, 7.12, 3.87, 3.48, 2.82;

¹³C NMR (DMSO) δ 166.13, 163.93, 130.55, 130.20, 115.15, 55.24, 55.97, 33.47.

EXAMPLE 5 Preparation of N-hydroxy-2-[(4-chlorobenzenesulfonyl)methyl]-3-(4-chlorobenzenesulfonyl)-propionamide.



Step 1 Preparation of 2-(4-chlorobenzenesulfonylmethyl)-3-(4-chlorobenzenesulfonyl)-propionic acid.

Following the general procedure in EXAMPLE 4 (steps 1 and 2) and making non-critical variations but starting with 4-chlorothiophenol in step 1, the title compound is obtained as a white solid.

m.p. 197° C (dec.);

¹H NMR (DMSO) δ 7.77, 7.67, 3.74, 3.54, 2.58;

¹³C NMR (DMSO) δ 171.24, 139.38, 138.34, 130.26, 129.91, 56.66, 37.59.

Step 2 Preparation of N-hydroxy-2-[(4-chlorobenzenesulfonyl)methyl]-3-(4-chlorobenzenesulfonyl)-propionamide.

A mixture of 2-(4-chlorobenzenesulfonylmethyl)-3-(4-chlorobenzenesulfonyl)-

propionic acid (0.52 g, 1.1 mmol), 1-hydroxybenzotriazole hydrate (0.16 g, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.25 g, 1.3 mmol), and hydroxylamine hydrochloride (0.083 g, 1.2 mmol) is stirred in an ice bath for 20 minutes and 4-methylmorpholine (0.28 mL, 2.5 mmol) in dimethylformamide (10 mL) is added. After stirring overnight at ambient temperature, the mixture is partitioned between ethyl acetate and aqueous 10% hydrochloric acid. The organic phase is further extracted with aqueous acid, aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*. The concentrate is chromatographed over silica gel (230-400 mesh) with chloroform/acetone/acetic acid (79/20/1) and the eluate concentrated *in vacuo*, to yield the title compound as a white solid.

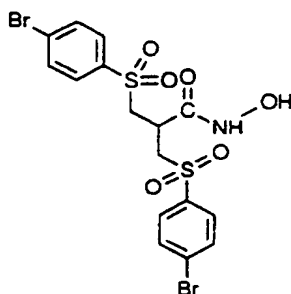
m.p. 196-7.5° C;

MS (FAB) *m/z* 452, 439, 437, 278, 243, 161, 159, 111;

¹H NMR (DMSO) δ 10.8, 8.93, 7.78, 7.70, 3.59, 2.77;

¹³C NMR (DMSO) δ 165.72, 140.09, 138.08, 130.66, 130.48, 56.01, 33.67.

EXAMPLE 6 Preparation of N-hydroxy-2-[(4-bromobenzenesulfonyl)methyl]-3-(4-bromobenzenesulfonyl)-propionamide.



Following the general procedure outlined in EXAMPLE 5 (steps 1 and 2) and making non-critical variations but starting with 4-bromothiophenol in step 1, the title compound is obtained as a white solid.

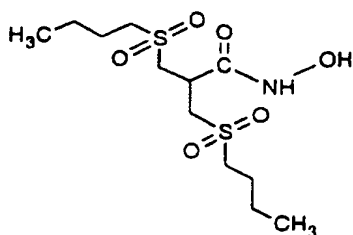
m.p. 187° C dec.;

MS (FAB) *m/z* 469, 421, 291, 245, 71, 69, 57, 55, 43, 41;

¹H NMR (DMSO) δ 10.9, 8.96, 7.85, 7.70, 3.61, 2.79;

¹³C NMR (DMSO) δ 165.75, 138.55, 133.42, 130.67, 129.25, 56.01, 33.65.

EXAMPLE 7 Preparation of N-hydroxy-2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionamide.



5

Step 1 Preparation of 2-[(n-butylthio)methyl]-3-(n-butylthio)-propionic acid, ethyl ester.

10 A mixture of 4-bromomethylacrylic acid, ethyl ester (1.0 g, 6.0 mmol), n-butylthiol (1.4 mL, 13 mmol), potassium carbonate (1.7 g, 13 mmol) in absolute ethyl alcohol (25 mL) is stirred at ambient temperature overnight. The mixture is transferred to ethyl acetate, extracted with aqueous 10% hydrochloric acid, and concentrated *in vacuo*, to afford the title compound as a clear, colorless oil.

15 ^1H NMR (DMSO) δ 4.07, 2.72, 2.47, 1.47, 1.36, 1.18, 0.86;

^{13}C NMR (DMSO) δ 173.08, 60.65, 46.36, 32.89, 31.61, 21.72, 14.52, 13.90.

Step 2 Preparation of 2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionic acid, ethyl ester.

20 After cooling a stirred mixture of 2-[(n-butylthio)methyl]-3-(n-butylthio)-propanoic acid, ethyl ester (1.0 g, 3.4 mmol) in methylene chloride (30 mL), m-chloroperoxybenzoic acid (3.0 g; 14. mmol) is added and the mixture is stirred overnight at ambient temperature. The mixture is filtered and the filtrate concentrated *in vacuo* to afford 2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propanoic acid, ethyl ester as a clear, colorless oil.

25 ^1H NMR (DMSO) δ 4.10, 3.51, 3.38, 3.14, 1.63, 1.39, 1.18, 0.85;

^{13}C NMR (DMSO) δ 170.99, 61.79, 52.82, 52.53, 34.20, 23.72, 21.40, 14.22, 13.89.

Step 3 Preparation of 2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionic acid.

30 A mixture of 2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propanoic acid, ethyl ester (1.0 g, 3.0 mmol) in 6N hydrochloric acid (20 mL) is refluxed overnight. The mixture is transferred to distilled water and extracted with ethyl acetate. The combined organic extracts are concentrated *in vacuo* to yield the title compound as a clear, colorless oil.

^1H NMR (DMSO) δ 3.50, 3.30, 3.14, 1.62, 1.37, 0.87;

35 ^{13}C NMR (DMSO) δ 172.33, 52.88, 52.48, 34.49, 23.75, 21.41, 13.88.

Step 4 Preparation of N-hydroxy-2-[(n-butylsulfonyl)methyl]-3-(n-

butylsulfonyl)-propionamide.

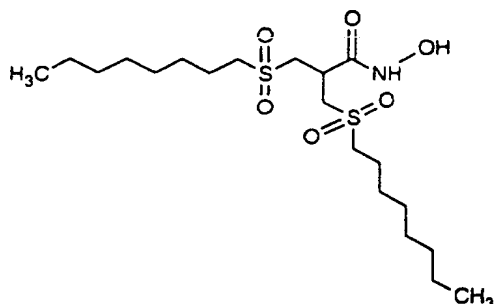
Following the general procedure outlined in EXAMPLE 4 (steps 3 and 4) and making non-critical variations but starting with 2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionic acid in step 3, the title compound is obtained as a white solid.

^1H NMR (DMSO) δ 10.9, 9.0, 3.37, 3.15, 3.09, 1.63, 1.38, 0.88;

^{13}C NMR (DMSO) δ 166.52, 52.93, 52.55, 32.58, 23.73, 21.43, 13.90.

EXAMPLE 8

Preparation of N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(n-octylsulfonyl)-propionamide.



Following the general procedure outlined in EXAMPLE 7 (steps 1 to 4) and making non-critical variations but starting with n-octylthiol in step 1, the title compound is obtained as a white solid.

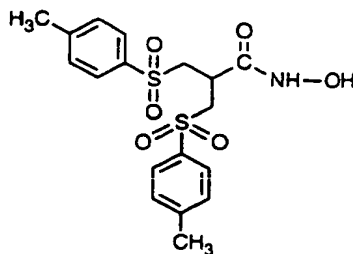
^1H NMR (DMSO) δ 10.9, 9.05, 3.40, 3.08, 1.61, 1.32, 1.23, 0.84;

MS (FAB) m/z 456, 440, 245, 133, 71, 69, 57, 55, 43, 41;

^{13}C NMR (DMSO) δ 166.53, 52.92, 52.77, 32.60, 31.64, 28.90, 28.87, 28.14, 22.51, 21.71, 14.40.

EXAMPLE 9

Preparation of N-hydroxy-2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-propionamide.



Step 1 Preparation of 2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)propionic acid.

A mixture of 2-bromomethylacrylic acid (2.0 g, 12 mmol), p-toluenesulfinic acid, sodium salt, monohydrate (6.4 g, 27 mmol), and sodium bicarbonate (1.0 g, 12 mmol) in toluene (50 mL) is refluxed overnight. The mixture is transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid. The organic phase is concentrated *in vacuo*, and triturated with hexane to yield the title compound as a white solid.

^1H NMR (DMSO) δ 7.66, 7.41, 3.47, 2.82, 2.69;

^{13}C NMR (DMSO) δ 171.46, 145.33, 135.72, 130.44, 128.29, 55.47, 36.15, 21.60.

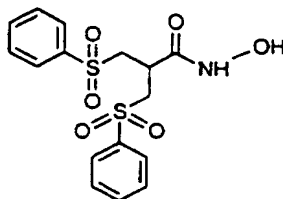
Step 2 Preparation of N-hydroxy-2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-propionamide.

To N-methylpyrrolidinone (20 mL) cooled in an ice bath, is added 2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-propionic acid (4.4 g, 11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.2 g, 22 mmol), and hydroxylamine hydrochloride (1.5 g, 22 mmol). After stirring overnight at ambient temperature, the mixture is transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid, distilled water, aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. The organic phase is concentrated *in vacuo* and triturated from hexane to afford the title compound as a white solid.

^1H NMR (DMSO) δ 10.9, 8.9, 7.62, 7.41, 3.47, 2.82, 2.42;

^{13}C NMR (DMSO) δ 165.94, 145.12, 136.19, 130.42, 128.37, 55.87, 33.34, 21.61.

EXAMPLE 10 Preparation of N-hydroxy-2-[(benzenesulfonyl)methyl]-3-(benzenesulfonyl)-propionamide.



Following the general procedure outlined in EXAMPLE 9 and making non-critical variations but starting with benzenesulfinic acid, sodium salt (2.5 g, 15 mmol) in step 1, the title compound is afforded as a white solid.

Found: C, 50.06; H, 4.56; N, 3.7; S, 16.44;

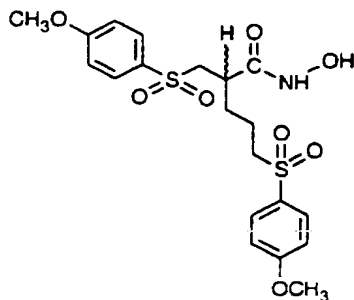
MS (FAB) m/z 386, 385, 384, 383, 351, 279, 242, 209, 149, 125;

^1H NMR (DMSO) δ 10.9, 8.9, 7.75, 7.66, 3.53, 2.86;

^{13}C NMR (DMSO) δ 165.83, 139.03, 134.62, 130.02, 128.21, 55.77, 33.19.

5 **EXAMPLE 11** Preparation of N-hydroxy-2-[(4-methoxybenzenesulfonyl)-methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide.

10



15 **Step 1** Preparation of 3-(4-methoxybenzenethio)-propylmalonic acid, diethyl ester.

To a stirred mixture of 3-chloropropylmalonic acid, diethyl ester (2.1 g, 8.6 mmol) in dimethylformamide (20 mL) is added 4-methoxybenzenethiol (1.2 mL, 9.5 mmol) in dimethylformamide (20 mL) and sodium bicarbonate (0.72 g, 8.6 mmol).

20 After stirring overnight at room temperature the mixture is transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid, distilled water, aqueous sodium bicarbonate, brine, and concentrated *in vacuo*. The concentrate is triturated with hexane, extracted with distilled water, concentrated *in vacuo*, and chromatographed over silica gel with methylene chloride/hexane (9/1) to yield the
25 title compound as a clear, colorless oil.

^1H NMR (DMSO) δ 7.29, 6.89, 4.08, 3.73, 3.45, 2.83, 1.85, 1.49, 1.14;

^{13}C NMR (DMSO) δ 169.66, 159.19, 133.05, 126.51, 115.52, 61.66, 55.99, 51.48, 34.65, 28.00, 27.01, 14.70.

30 **Step 2** Preparation of 3-(4-methoxybenzenesulfonyl)-propylmalonic acid, diethyl ester.

A stirred mixture of 3-(4-methoxybenzenethio)-propylmalonic acid, diethyl ester (2.4 g, 7.0 mmol) in chloroform (150 mL) is cooled and m-chloroperoxybenzoic acid (3.3 g, 15 mmol) is added in small portions. After stirring overnight at ambient temperature, the mixture is transferred to chloroform/methyl alcohol (9/1) and
35 extracted with aqueous sodium bicarbonate, brine, and concentrated *in vacuo*. The concentrate is chromatographed over silica gel using chloroform/methyl alcohol

(99.5/0.5), and the eluate concentrated *in vacuo* to yield the title compound as a clear, colorless oil.

^1H NMR (DMSO) δ 7.77, 7.14, 4.06, 3.84, 3.49, 3.26, 1.79, 1.51, 1.11;

^{13}C NMR (DMSO) δ 169.16, 163.67, 130.92, 115.04, 61.36, 56.23, 54.84, 50.90, 27.03,

5 20.69, 14.32.

Step 3 Preparation of 3-(4-methoxybenzenesulfonyl)-propylmalonic acid, monoethyl ester.

To a stirred mixture of 3-(4-methoxybenzenesulfonyl)-propylmalonic acid, diethyl ester (2.0 g, 5.4 mmol) in absolute ethyl alcohol (50 mL) is added potassium
10 hydroxide (0.41 g, 5.9 mmol) in absolute ethyl alcohol. After stirring overnight at ambient temperature, the mixture is partitioned between chloroform/methyl alcohol (9/1) and aqueous sodium hydroxide. The aqueous phase is acidified with concentrated hydrochloric acid, extracted with chloroform/methyl alcohol (9/1), and the organic extracts concentrated *in vacuo* to yield the title compound as a clear,
15 colorless oil.

^1H NMR (DMSO) δ 7.18, 7.15, 4.06, 3.85, 3.36, 3.27, 1.80, 1.54, 1.13;

^{13}C NMR (DMSO) δ 170.97, 169.99, 164.03, 131.32, 130.73, 61.54, 56.60, 55.33, 51.57, 27.53, 21.17, 14.73.

Step 4 Preparation of 2-[(4-methoxybenzenesulfonyl)propyl]-2-propenoic acid, ethyl ester.
20

A mixture of 3-(4-methoxybenzenesulfonyl)-propylmalonic acid, monoethyl ester (1.1 g, 3.2 mmol), paraformaldehyde (0.11 g, 3.5 mmol), piperidine (0.03 mL, 0.32 mmol), and pyridine (20 mL) is refluxed for three hours. The mixture is transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid,
25 distilled water, aqueous sodium bicarbonate, brine, and the organic phase is concentrated *in vacuo* to yield the title compound as a clear, colorless oil.

^1H NMR (DMSO) δ 7.79, 7.15, 6.05, 5.59, 4.09, 3.84, 3.21, 2.29, 1.67, 1.16;

^{13}C NMR (DMSO) δ 166.80, 164.05, 139.74, 131.30, 130.78, 126.72, 115.44, 61.17, 56.61, 55.23, 30.45, 22.33, 14.80.

Step 5 Preparation of 2-[(4-methoxybenzenethio)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid, ethyl ester.
30

To a stirred mixture of 4-methoxybenzenethiol (0.30 mL, 2.2 mmol) in absolute ethyl alcohol (1 mL) cooled in an ice bath, is added sodium ethoxide solution (0.2 mL, 0.22 mmol) followed in fifteen minutes by 2-[(4-methoxybenzenesulfonyl) propyl]-2-propenoic acid, ethyl ester (0.70 g, 2.2 mmol) in
35 absolute ethyl alcohol (2 mL). After stirring overnight at ambient temperature, the

mixture is transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid, distilled water, aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The concentrate is triturated with hexane, the filtered solids extracted with chloroform and concentrated *in vacuo* to yield the title compound as a white solid.

^1H NMR (DMSO) δ 7.76, 7.31, 7.14, 6.86, 3.96, 3.83, 3.72, 3.16, 2.90, 2.40, 1.58, 1.44, 1.08;

^{13}C NMR (DMSO) δ 173.70, 163.70, 159.18, 133.49, 130.87, 125.42, 115.23, 115.04, 60.56, 56.23, 55.66, 55.00, 45.05, 37.08, 29.88, 20.81, 14.48.

- 10 Step 6 Preparation of 2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid, ethyl ester.

To a stirred mixture of 2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid, ethyl ester (0.8 g, 1.8 mmol) in chloroform (50 mL) cooled in an ice bath, is added m-chloroperoxybenzoic acid (0.81 g, 3.7 mmol). After stirring overnight at ambient temperature, the mixture is transferred to ethyl acetate which is extracted with aqueous sodium bicarbonate and brine. The organic phase is concentrated *in vacuo*, triturated with hexane, and the filtered solids dissolved in chloroform. The chloroform mixture is then extracted with aqueous sodium bicarbonate and brine and the organic phase is concentrated *in vacuo* to yield the title compound as a white solid.

^1H NMR (DMSO) δ 7.75, 7.15, 3.89, 3.85, 3.50, 3.39, 3.16, 2.59, 1.57, 1.42, 1.57, 1.41, 1.08;

^{13}C NMR (DMSO) δ 172.94, 164.27, 164.06, 131.21, 130.95, 130.73, 115.46, 61.37, 57.29, 56.66, 56.62, 55.17, 30.78, 20.81, 14.65.

- 25 Step 7 Preparation of 2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid.

A mixture of 2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid, ethyl ester (0.70 g, 1.4 mmol) in 6N hydrochloric acid (20 ml) is refluxed overnight. The mixture is transferred to ethyl acetate which is extracted with aqueous sodium bicarbonate. The combined aqueous extract is acidified with concentrated hydrochloric acid and extracted with ethyl acetate. This organic extract is concentrated *in vacuo* to yield the title compound as a white solid.

^1H NMR (DMSO) δ 12.5, 7.77, 7.14, 3.85, 3.50, 3.32, 3.16, 2.49, 1.57, 1.45;

35 ^{13}C NMR (DMSO) δ 174.41, 164.20, 164.03, 131.29, 131.17, 130.90, 130.67, 115.45, 80.03, 57.24, 56.62, 55.28, 30.68, 20.73.

Step 8 Preparation of N-benzyloxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide.

A mixture of 2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanoic acid (0.5 g, 1.1 mmol), benzylhydroxylamine hydrochloride (0.21 g, 1.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.42 g, 2.2 mmol), and tetrahydrofuran/water (1/1, 10 mL) is stirred at ambient temperature overnight. The mixture is transferred to ethyl acetate which is extracted with aqueous 10% hydrochloric acid, distilled water, aqueous sodium bicarbonate, and brine. The organic phase is concentrated *in vacuo* to yield the title compound as a white solid.

^1H NMR (DMSO) δ 11.2, 7.76, 7.37, 7.12, 4.60, 3.84, 3.78, 3.50, 3.22, 3.10, 2.39, 1.48, 1.35.

Step 9 Preparation of N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide.

A mixture of N-benzyloxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide (0.3 g, 0.5 mmol), Pearlman's catalyst (0.11 g), and absolute ethyl alcohol is agitated under hydrogen (15 psig) overnight at room temperature. The mixture is filtered and the filtrate is concentrated *in vacuo*. The concentrate is chromatographed over silica gel with chloroform/ethyl acetate/methyl alcohol/acetic acid (50/40/10/1) and the eluate concentrated *in vacuo* to afford the title compound as a white solid.

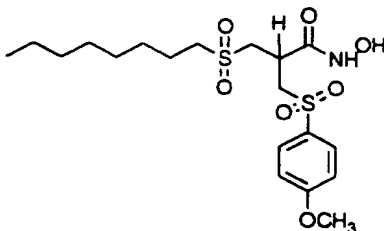
IR (mull) 1667, 1596, 1578, 1499, 1317, 1294, 1263, 1141, 1089, 1024, 837, cm^{-1} ;

MS (FAB) m/z 473, 472, 391, 371, 149, 129, 71, 57, 55, 43;

Specific Rotation $[\alpha]^{25}_{\text{D}} = 0$;

^1H NMR (DMSO) δ 10.5, 8.8, 7.76, 7.14, 3.86, 3.42, 3.18, 2.3, 1.46.

EXAMPLE 12 Preparation of N-hydroxy-2-(n-octylsulfonylmethyl)-3-(4-methoxybenzenesulfonyl)-propionamide.



Step 1 Preparation of 2-[(n-octylthio)methyl]-2-propenoic acid.

A mixture of 2-bromomethylacrylic acid (1.0 g, 6.0 mmol), n-octylthiol (1.2 mL, 6.6 mmol), and dimethylformamide (10 mL) is refluxed overnight. The mixture is then transferred to ethyl acetate and extracted with aqueous 10% hydrochloric acid and distilled water. The organic phase is concentrated *in vacuo* to afford the
5 title compound as a white solid.

¹H NMR (DMSO) δ 6.00, 5.60, 3.27, 2.37, 1.46, 1.28, 1.22, 0.84;

¹³C NMR (DMSO) δ 167.62, 138.23, 125.42, 32.28, 31.69, 31.07, 29.15, 29.06, 29.02, 28.70, 22.53, 14.37.

Step 2 Preparation of 2-[(n-octylthio)methyl]-3-(4-methoxybenzenethio)-
10 propenoic acid.

A mixture of 2-[(n-octylthio)methyl]-2-propenoic acid (1.0 g, 4.3 mmol), 4-methoxybenzenethiol (1.1 mL, 8.6 mmol), and dimethylformamide (25 mL) is refluxed overnight. The mixture is partitioned between ethyl acetate and aqueous 10% hydrochloric acid and the organic phase is concentrated *in vacuo*. The
15 concentrate is chromatographed over silica gel using chloroform/methyl alcohol/acetic acid (98/1/1) and the eluate is concentrated in *vacuo* to yield the title compound as a white solid.

¹H NMR (DMSO) δ 12.5, 7.36, 6.90, 3.73, 3.04, 2.72, 2.55, 2.38, 1.42, 1.21, 0.84;

¹³C NMR (DMSO) δ 174.76, 159.53, 133.66, 152.92, 152.65, 115.58, 55.98, 46.02,
20 36.80, 33.12, 32.28, 32.07, 29.87, 29.55, 29.47, 29.39, 22.93, 14.75.

Step 3 Preparation of 2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)propionic acid.

To a stirred mixture of 2-[(n-octylthio)methyl]-3-(4-methoxybenzenethio)-propionic acid (0.6 g, 1.6 mmol) in chloroform (15 mL) cooled in an ice bath, is
25 added m-chloroperoxybenzoic acid (1.4 g, 6.6 mmol). After stirring at ambient temperature overnight, the mixture is partitioned between hexane and aqueous 10% hydrochloric acid and the aqueous phase is further extracted with hexane and with ethyl acetate. The ethyl acetate extract is concentrated *in vacuo* and chromatographed over silica gel with chloroform/methyl alcohol/acetic acid (98/1/1) to yield
30 the title compound as a white solid.

¹H NMR (DMSO) δ 7.80, 7.17, 3.68, 3.61, 3.49, 3.38, 3.02, 1.59, 1.32, 1.23, 0.85.

Step 4 Preparation of N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide.

Following the general procedure outlined in EXAMPLE 4 (steps 3 and 4) and
35 making non-critical variations but starting with 2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionic acid (0.5 g, 1.2 mmol) in step 3, the title

compound is obtained as a white solid.

m.p. 134.5 °C;

MS (FAB) m/z 451, 450, 434, 239, 133, 57, 43, 41, 39;

¹H NMR (DMSO) δ 10.9, 8.9, 7.80, 7.15, 3.86, 3.73, 3.50, 3.01, 2.70, 2.36, 1.55, 1.08,

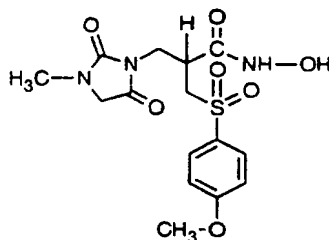
5 0.82;

¹³C NMR (DMSO) δ 166.20, 163.90, 130.82, 130.58, 115.13, 60.87, 56.27, 52.90,

52.68, 44.69, 32.98, 31.63, 28.87, 28.13, 22.51, 21.63, 14.40.

EXAMPLE 13 Preparation of N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

10



15

Step 1 Preparation of 2-[methyl-3-(1-methylhydantoin)]-2-propenoic acid.

20 A mixture of 2-bromomethylacrylic acid (1.0 g, 6.0 mmol), 1-methylhydantoin (0.85 g, 7.2 mmol), sodium bicarbonate (1.1 g, 13 mmol), and toluene (50 mL) is refluxed overnight. The mixture is transferred to ethyl acetate and extracted with aqueous sodium bicarbonate. The aqueous phase is acidified with concentrated hydrochloric acid and extracted with ethyl acetate and chloroform/methyl alcohol (9/1). Concentration of the organic extracts yields the title compound as a solid.

25

¹H NMR (DMSO) δ 6.08, 5.47, 4.08, 4.00, 2.85.

Step 2 Preparation of 2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenethio)-propionic acid.

30 A mixture of 2-methenyl-2-[methyl-3-(1-methylhydantoin)]-propenoic acid (1.1 g, 5.5 mmol), 4-methoxybenzenethiol (0.75 mL, 6.0 mmol), sodium bicarbonate (0.92 g, 11 mmol), and toluene (50 mL) is refluxed overnight. The mixture is concentrated *in vacuo* and chromatographed over silica gel using chloroform/methyl alcohol/acetic acid (97/2/1). The eluate is concentrated *in vacuo* and triturated with hexane to yield the title compound as a white solid.

35

¹H NMR (DMSO) δ 12.3, 7.33, 6.90, 3.92, 3.74, 3.60, 2.95, 2.83, 2.74;

¹³C NMR (DMSO) δ 173.90, 171.02, 159.58, 156.98, 133.87, 152.92, 115.61, 56.02,

62.01, 44.45, 40.13, 35.63, 30.01.

Step 3 Preparation of 2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionic acid.

A mixture of 2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenethio)-
5 propionic acid (1.0 g, 3.0 mmol) in methylene chloride (50 mL) is cooled and m-chloroperoxybenzoic acid (1.4 g, 6.3 mmol) is added. After stirring at ambient temperature overnight, the mixture is concentrated *in vacuo* and chromatographed over silica gel 60 (230-400 mesh) using chloroform/methyl alcohol/acetic acid (94/5/1). The eluate is concentrated *in vacuo* to yield the title compound as a white solid.
10 ¹H NMR (DMSO) δ 7.75, 7.14, 3.87, 3.84, 3.54, 3.35, 2.92, 2.80.

Step 4 Preparation of N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

Following the general procedure outlined in EXAMPLE 4 (steps 3 and 4) and making non-critical variations but starting with 2-[methyl-3-(1-methylhydantoin)]-3-
15 (4-methoxybenzenesulfonyl)-propionic acid (0.6 g, 1.6 mmol) in step 3 the title compound is obtained.

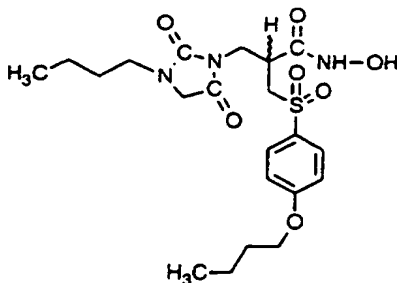
MS (EI) *m/z* 385 (M⁺), 214, 181, 172, 171, 155, 123, 107, 99, 77, 56;

¹H NMR (DMSO) δ 10.8, 8.2, 7.76, 7.13, 3.84, 3.44, 3.24, 2.81;

¹³C NMR (DMSO) δ 170.68, 166.39, 163.77, 156.41, 130.72, 130.51, 115.06, 56.26,
20 54.99, 51.68, 39.68, 37.24, 29.66.

EXAMPLE 14 Preparation of N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide.

25



30

Step 1 Preparation of 4-butoxybenzenesulfinic acid, sodium salt.

To a stirred mixture of sodium iodide (8.8 g, 59 mmol) in acetone (250 mL) is
35 added 4-butoxybenzenesulfonyl chloride (5.0 g, 20 mmol). After stirring at ambient temperature overnight, the mixture is filtered and the filtered solids washed with

acetone to afford 4-butoxybenzenesulfinic acid, sodium salt as a white solid.

^1H NMR (DMSO) δ 7.49, 6.81, 3.93, 1.67, 1.40, 0.90.

Step 2 Preparation of 2-[(4-butoxybenzenesulfonyl)methyl]-2-propenoic acid.

A mixture of 2-bromomethylacrylic acid (1.0 g, 6.0 mmol), 4-butoxybenzenesulfinic acid, sodium salt (3.1 g, 13 mmol), sodium carbonate (1.9 g, 18 mmol) and dimethylformamide (20 mL) is refluxed overnight. The reaction mixture is then partitioned between ethyl acetate and aqueous 10% hydrochloric acid and the organic phase is concentrated *in vacuo*. The concentrate is chromatographed over silica gel 60 (230-400 mesh) with chloroform/methyl alcohol/acetic acid (94/5/1) and the eluate concentrated *in vacuo* to afford the title compound as a white solid.

^1H NMR (DMSO) δ 12.9, 7.67, 7.10, 6.28, 5.70, 4.22, 4.03, 1.68, 1.41, 0.90;

^{13}C NMR (DMSO) δ 167.04, 163.63, 133.06, 131.33, 130.91, 130.47, 114.08, 68.69, 57.60, 31.33, 19.48, 14.47.

Step 3 Preparation of 2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionic acid.

A mixture of 2-[(4-butoxybenzenesulfonyl)methyl]-2-propenoic acid (1.0 g, 3.4 mmol), 1-butylhydantoin (0.78 g, 5.0 mmol), sodium bicarbonate (0.63 g, 7.4 mmol), and toluene (50 mL) is refluxed overnight. The reaction mixture is transferred to ethyl acetate, extracted with aqueous 10% hydrochloric acid, and concentrated *in vacuo*. The concentrate is triturated with hexane and diethyl ether to yield the title compound as a white solid.

^1H NMR (DMSO) δ 7.73, 7.14, 5.74, 4.07, 3.90, 3.59, 3.54, 3.23, 2.95, 1.72, 1.42, 1.24, 0.93, 0.87;

^{13}C NMR (DMSO) δ 172.46, 171.21, 163.73, 156.53, 130.89, 130.63, 115.88, 68.73, 55.72, 55.52, 49.94, 42.42, 31.32, 29.83, 20.02, 19.47, 14.47, 14.34.

Step 4 Preparation of N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide.

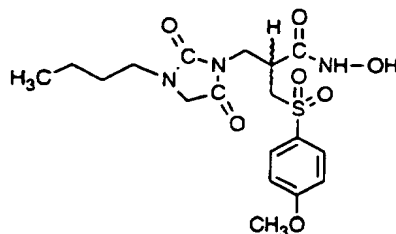
Following the general procedure outlined in EXAMPLE 4 (steps 3 and 4) and making non-critical variations but starting with 2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionic acid (0.59 g, 1.3 mmol) in step 3 the title compound is obtained as a white solid.

MS (FAB) m/z 471, 470, 469, 223, 197, 149, 57, 41, 23;

^1H NMR (DMSO) δ 10.8, 8.8, 7.74, 7.10, 5.73, 4.06, 3.88, 3.47, 3.21, 2.82, 1.71, 1.42, 1.25, 0.92, 0.87.

EXAMPLE 15 Preparation of N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

5



10 Following the general procedure outlined in EXAMPLE 14 (steps 1 to 4) and making non-critical variations but starting with 4-methoxybenzenesulfonyl chloride in step 1, the title compound is obtained as a white solid.

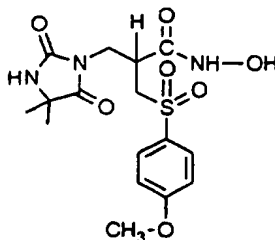
MS (FAB) m/z 428 (MH⁺), 429, 428, 223, 149, 129, 71, 57, 55, 43, 41;

¹H NMR (DMSO) δ 10.80, 8.81, 7.77, 7.12, 3.85, 3.49, 3.23, 2.83, 1.43, 1.24, 0.88;

15 ¹³C NMR (DMSO) δ 170.79, 166.40, 163.77, 156.17, 130.78, 130.47, 115.08, 55.26, 55.08, 46.63, 42.10, 41.2, 37.25, 29.49, 19.68, 13.99.

EXAMPLE 16 Preparation of N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

20



25

30 Following the general procedure outlined in EXAMPLE 14 (steps 1 to 4) and making non-critical variations but starting with 5,5-dimethylhydantoin (1.5 g, 11 mmol) in step 3, the title compound is obtained as a white solid.

¹H NMR (DMSO) δ 10.8, 8.2, 7.77, 7.12, 3.84, 3.41, 3.17, 2.85, 1.21;

¹³C NMR (DMSO) δ 177.62, 166.35, 163.82, 155.28, 130.85, 130.49, 115.14, 58.16, 56.26, 55.37, 37.20, 24.95, 24.87.

35

EXAMPLE 17 Preparation of (+)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-

methoxybenzenesulfonyl)-propionamide and (-)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)propionamide.

5 A racemic mixture of N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(n-octylsulfonyl)propionamide (EXAMPLE 12) is eluted over a Chiralpak AD, column with absolute ethyl alcohol and the eluates collected at $R_f = 13.5$ minutes and $R_f = 23.5$ minutes are concentrated *in vacuo* to yield an enantiomer (17A) ($[\alpha]_D^{25} = +4^\circ$) and an enantiomer (17B) ($[\alpha]_D^{25} = -4^\circ$), respectively.

10 EXAMPLE 18 Preparation of (+)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide and (-)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

15 A racemic mixture of N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide (EXAMPLE 13) is eluted over a Chiralpak AD, column with absolute ethyl alcohol and the eluates collected at $R_f = 8.6$ minutes and $R_f = 10.5$ minutes are concentrated *in vacuo* to yield the enantiomers, 18A and 18B, respectively.

20 EXAMPLE 19 Preparation of (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide and (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide.

25 A racemic mixture of N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide (EXAMPLE 14) is eluted over a Chiralpak AD column with absolute ethyl alcohol and the eluates collected at $R_f = 16.5$ minutes and $R_f = 17.8$ minutes are concentrated *in vacuo* to yield an enantiomer (19A) ($[\alpha]_D^{25} = -3^\circ$) and an enantiomer (19B) ($[\alpha]_D^{25} = +3^\circ$), respectively.

30 EXAMPLE 20 Preparation of (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide and (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

35 A racemic mixture of N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide (EXAMPLE 15) is eluted over a Chiralpak AD column with absolute ethyl alcohol and the eluates collected at $R_f = 13.4$

minutes and $R_f = 15.8$ minutes are concentrated *in vacuo* to yield an enantiomer (20A) ($[\alpha]_D^{25} = -4^\circ$) and an enantiomer (20B) ($[\alpha]_D^{25} = +4^\circ$), respectively.

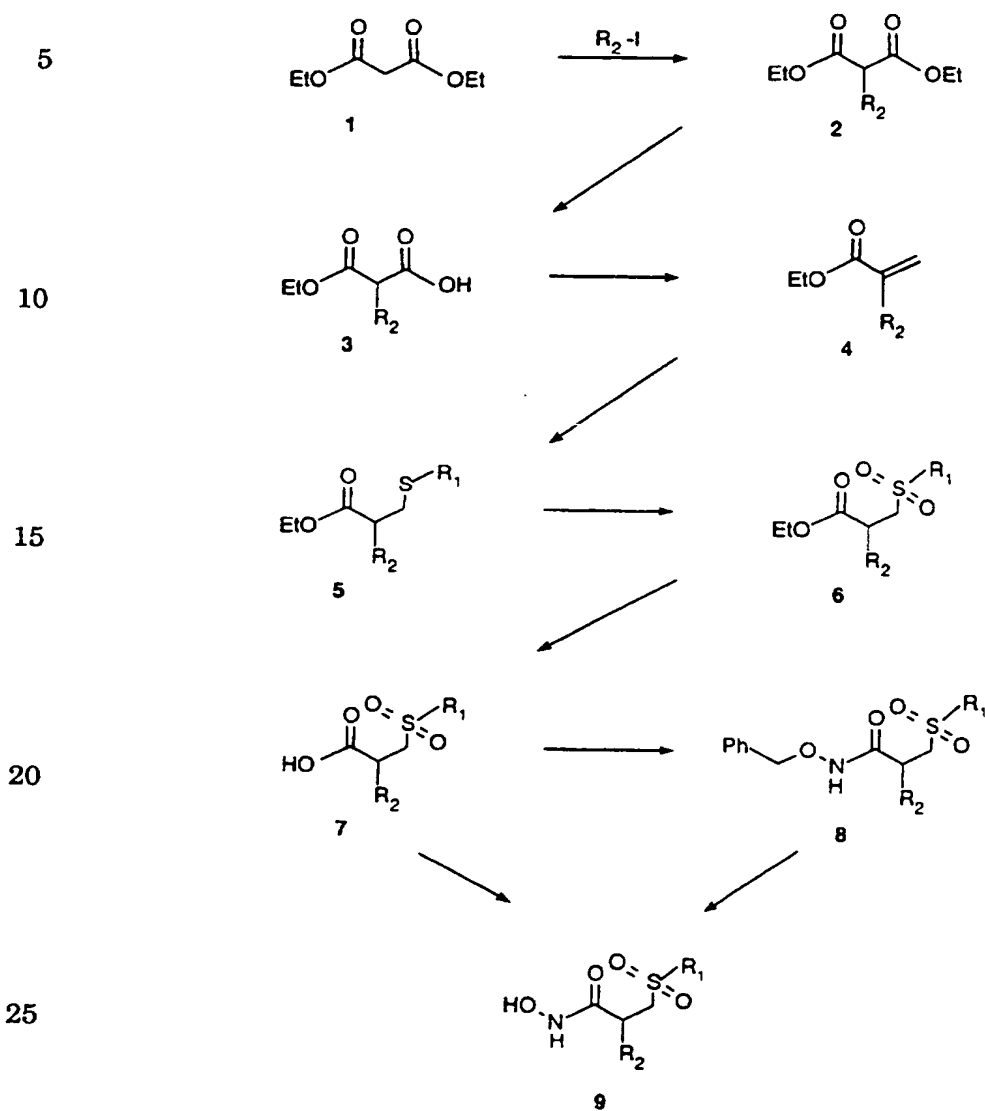
EXAMPLE 21**Biological Activity Test**

5 Inhibitory activity is evaluated in one or more of the MMP enzymes (stromelysin, gelatinase, and collagenase) in vitro using particle concentration fluorescence assay. An inhibitor binds to MMP enzymes which prevents the degradation of a substrate by stromelysin, gelatinase, or collagenase. The substrate has attached to it a fluorescein and a biotin moiety. The intact substrate then binds
10 to an avidin-coated particle via the biotin moiety. Once the particle is washed and dried, a fluorescent signal is generated since the fluorescent group is attached to the particle. Without an inhibitor present, the substrate is degraded by MMP enzymes and the fluorescein group is removed, therefore, no fluorescent signal can be detected. Testing compounds are dissolved in DMSO to the desired concentration,
15 then the solutions are diluted to 1:5 with MMP buffer (50 mM Tris-HCl, pH 7.5; 150 mM NaCl; 0.02% NaN₃). Serial two-fold dilutions of each compound are prepared. A concentrated, activated enzyme solution is transferred into each plate of the testing compounds, and the mixture is incubated at room temperature for 15 minutes. Thawed MMP substrate is then added into all plates, and the plates are
20 incubated in the dark for 1-3 hours at room temperature. At this point, the substrate mixture is mixed with 0.1% avidin-coated polystyrene particles. After 15 minutes, the fluorescence values are measured following filtration and washing of the beads. K_i values are then calculated. Inhibitory data for the compounds of this invention are shown in TABLE 1. Compounds with lower K_i values are expected to
25 be more effective as MMP inhibitors. It is expected that a compound with a K_i less than 15 μ M against stromelysin will display therapeutic effects in connective tissue disorders.

TABLE 1
MMP Inhibition Constants (K_i , μM) of the Compounds of the Invention

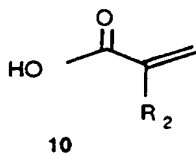
Example No.	Stromelysin K_i (μM)	Gelatinase K_i (μM)
1	0.049	0.0092
2	1.1	0.087
3	3.6	0.081
4	0.0039	0.00019
5	0.072	0.0019
6	0.092	0.0025
7	1	0.35
8	0.44	0.19
9	0.13	0.0038
10	0.16	0.008
11	0.001	0.001
12	0.0054	0.00082
13	0.017	0.0013
14	0.0018	0.000092
15	0.009	0.00034

SCHEME I

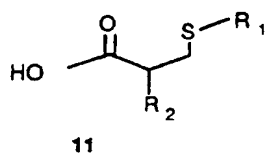


SCHEME II

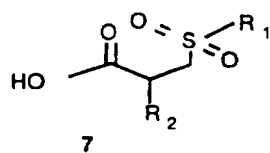
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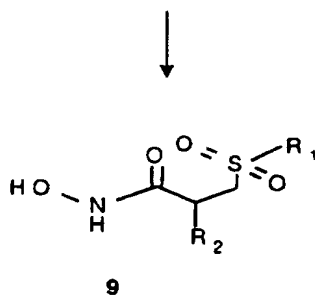
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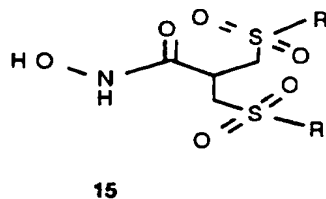
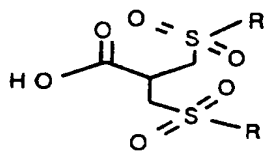
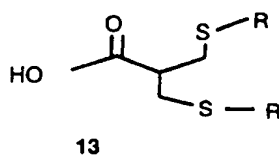
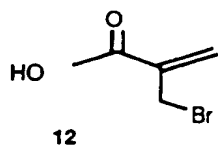
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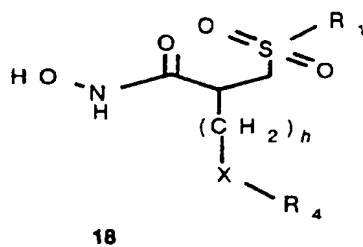
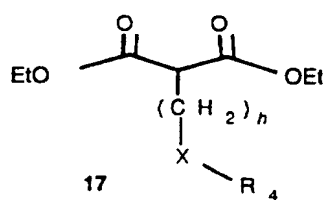
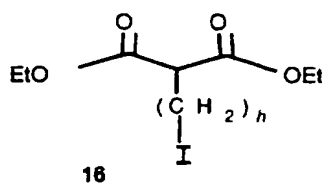
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SCHEME III



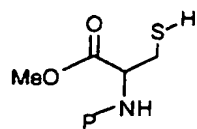
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SCHEME IV

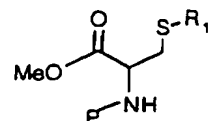


SCHEME V

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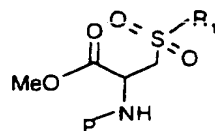


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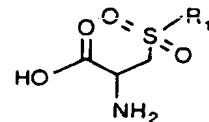


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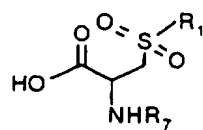


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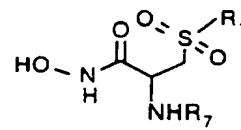


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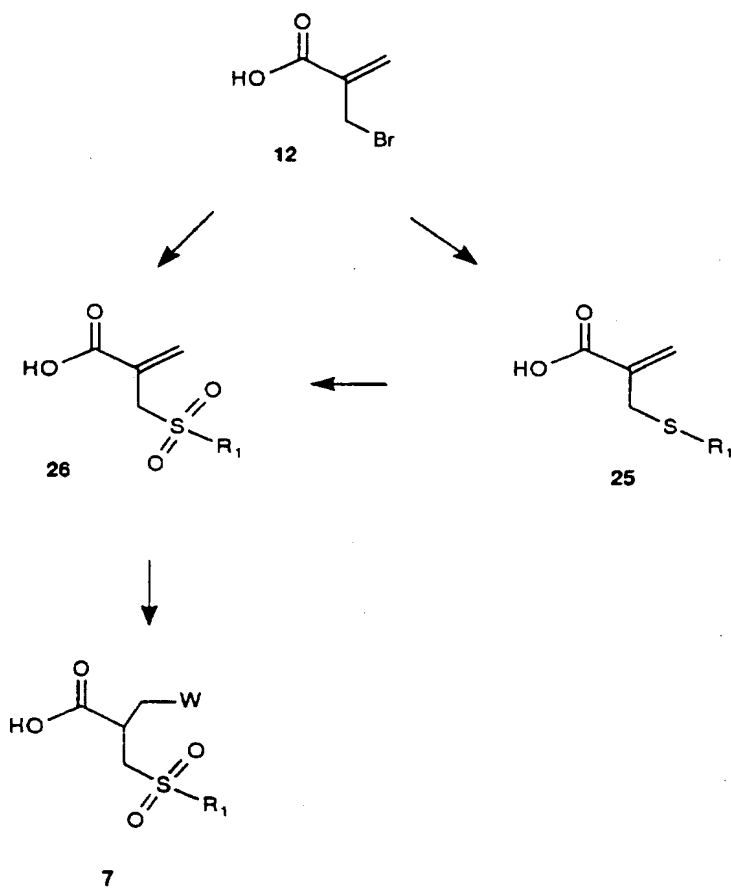


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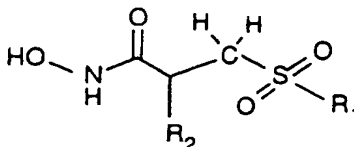
SCHEME VI



CLAIMS

We claim:

1. A compound of formula I



I

or pharmaceutical acceptable salts thereof wherein:

R₁ is

- a) C₄₋₁₂ alkyl,
- b) C₄₋₁₂ alkenyl,
- c) C₄₋₁₂ alkynyl,
- d) -(CH₂)_h-C₃₋₈ cycloalkyl,
- e) -(CH₂)_h-aryl,
- f) -(CH₂)_h-aryl substituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, halo, -NO₂, -CF₃, -CN, or -N(C₁₋₄ alkyl)₂,
- g) -(CH₂)_h-het, or
- h) -(CH₂)_h-het substituted with C₁₋₄ alkyl, or halo;

R₂ is

- a) C₁₋₁₂ alkyl,
- b) C₁₋₁₂ alkyl substituted with one to three halo, -CN, -NO₂, -CF₃, -N(R₃)₂, -SR₃, or OH,
- c) C₂₋₁₂ alkenyl,
- d) C₂₋₁₂ alkenyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- e) C₂₋₁₂ alkynyl,
- f) C₂₋₁₂ alkynyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- g) -(CH₂)_h-C₃₋₈ cycloalkyl,
- h) -(CH₂)_h-C₃₋₈ cycloalkyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo,
- i) -(CH₂)_h-C₃₋₈ cycloalkenyl,
- j) -(CH₂)_h-C₃₋₈ cycloalkenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo,

- k) $-(CH_2)_h$ -aryl,
 l) $-(CH_2)_h$ -aryl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, $-CF_3$, $-OH$, $-NO_2$, $-CN$, $-N(R_3)_2$, $-SR_3$, $-SO_2(C_{1-4} \text{ alkoxy})$, $-C(=O)R_3$, or $-NC(=O)R_3$,
 5 m) $-(CH_2)_h$ -aryl substituted with one to five halo,
 n) $-(CH_2)_h$ -het,
 o) $-(CH_2)_h$ -het substituted with one to two C_{1-4} alkyl, or halo,
 p) $-(CH_2)_h$ -Q,
 q) $-(CH_2)_h$ -Q substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo,
 10 or phenyl,
 r) $-(CH_2)_i$ -X- R_4 , optionally the $-(CH_2)_i$ - chain can be substituted with C_{1-4} alkyl or phenyl, which in turn can be substituted with one to three halo or C_{1-4} alkyl, or
 s) $-(CH_2)_i$ -CHR₅R₆;
 15 R_3 is
 a) H,
 b) C_{1-4} alkyl,
 c) $-(CH_2)_h$ -phenyl, or
 d) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy,
 20 or halo;
 X is
 a) -O-,
 b) $-S(=O)_j$ -,
 c) $-NR_7$ -,
 25 d) $-S(=O)_2NR_8$ -, or
 e) $-C(=O)$ -;
 R_4 is
 a) H,
 b) C_{1-4} alkyl,
 30 c) $-(CH_2)_h$ -phenyl,
 d) $-(CH_2)_h$ -phenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, $-NO_2$, or $-CN$, or
 e) $-(CH_2)_h$ -het;
 R_5 is
 35 a) C_{1-4} alkyl, or
 b) $-C(=O)R_3$;

R₆ is

- a) -C(=O)R₃, or
- b) -(CH₂)_hC(=O)R₃;

R₇ is

- 5 a) H,
- b) C₁₋₄ alkyl,
- c) -(CH₂)_h-phenyl,
- d) -(CH₂)_h-phenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo,
- 10 e) -C(=O)-R₃,
- f) -S(=O)₂R₃, or
- g) -C(=O)OR₃;

R₈ is

- a) C₁₋₄ alkyl,
- 15 b) -(CH₂)_h-phenyl, or
- c) -(CH₂)_h-phenyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

aryl is monocarbocyclic, or bicarbocyclic aromatic moiety;

het is 5- to 10-membered unsaturated heterocyclic moiety having one to three atoms
20 selected from the group consisting of oxygen, nitrogen, and sulfur;

Q is 5- to 10-membered saturated heterocyclic moiety having one to two atoms
selected from the group consisting of oxygen, nitrogen, and sulfur;

h is 0, 1, 2, 3, 4, 5, or 6;

i is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

25 j is 0, 1, or 2.

2. A compound of formula I according to claim 1 wherein

R₂ is

- a) C₁₋₁₂ alkyl substituted with one to three halo, -CN, -NO₂, -CF₃,
30 -N(R₃)₂, -SR₃, or OH,
- b) C₂₋₁₂ alkenyl,
- c) C₂₋₁₂ alkenyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- d) C₂₋₁₂ alkynyl,
- e) C₂₋₁₂ alkynyl substituted with one to three halo, -CN, -NO₂, or -CF₃,
- 35 f) -(CH₂)_h-C₃₋₈ cycloalkyl substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo,

- g) $-(CH_2)_h-C_{3-8}$ cycloalkenyl,
 h) $-(CH_2)_h-C_{3-8}$ cycloalkenyl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, or halo,
 i) aryl,
 5 j) aryl substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, $-CF_3$, $-OH$, $-NO_2$, $-CN$, $-N(R_3)_2$, $-SR_3$, $-SO_2(C_{1-4}$ alkoxy), $-C(=O)R_3$, or $-NC(=O)R_3$,
 k) $-(CH_2)_h$ -het,
 l) $-(CH_2)_h$ -het substituted with one to two C_{1-4} alkyl, or halo,
 10 m) $-(CH_2)_i-Q$,
 n) $-(CH_2)_i-Q$ substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, or phenyl,
 o) $-(CH_2)_i-X-R_4$, optionally the $-(CH_2)_i$ - chain can be substituted with C_{1-4} alkyl or phenyl, which in turn can be substituted with one to
 15 three halo or C_{1-4} alkyl, or
 p) $-(CH_2)_h-CHR_5R_6$;

wherein R_3 , X , R_4 , R_5 , R_6 , R_7 , R_8 , aryl, het and Q are as defined as in claim 1;

h is 0, 1, 2, 3, 4, 5, or 6; and

i is 1, 2, 3, 4, 5 or 6.

20

3. A compound of formula I according to claim 1 wherein

R_2 is

- a) $-(CH_2)_h$ -het,
 b) $-(CH_2)_h$ -het substituted with one to two C_{1-4} alkyl, or halo,
 25 c) $-(CH_2)_i-Q$,
 d) $-(CH_2)_i-Q$ substituted with one to three C_{1-4} alkyl, C_{1-4} alkoxy, halo, or phenyl, or
 e) $-(CH_2)_i-X-R_4$, optionally the $-(CH_2)_i$ - chain can be substituted with C_{1-4} alkyl or phenyl, which in turn can be substituted with one to
 30 three halo or C_{1-4} alkyl;

wherein X , R_4 , R_7 , R_8 , aryl, het and Q are as defined as in claim 1;

h is 0, 1, 2, 3, 4, 5, or 6; and

i is 1, 2, 3, 4, 5 or 6.

35

4. A compound of formula I according to claim 1 wherein

R₁ is

- a) C₄₋₈ alkyl,
- b) -(CH₂)_h-phenyl, or
- c) -(CH₂)_h-phenyl substituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluoro, chloro, or bromo;

R₂ is

- a) -(CH₂)_h-pyridyl, quinolinyl, pyrrolyl, thienyl, or thiazolyl, or indolyl, which can optionally be substituted with one to three C₁₋₄ alkyl, C₁₋₄ alkoxy, phenyl, fluoro, chloro, or bromo;
- b) -(CH₂)_h-piperdiny, piperazinyl, morpholino, 4-thiomorpholinyl, butyrolactamyl, 2-oxo-oxazolidinyl, or 2,4-dioxo-imidazolidinyl, which can optionally be substituted with one to three C₁₋₄ alkyl, phenyl, fluoro, chloro, or bromo;
- c) -(CH₂)_i-X-R₄;

X is

- a) -S(=O)_j,

R₄ is

- a) C₁₋₈ alkyl,
- b) phenyl, or
- c) phenyl substituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, or halo;

h is 0, 1, 2, 3, 4, 5 or 6;

i is 1, 2, 3, 4, 5 or 6; and

j is 0, 1 or 2.

5. A compound of claim 1 wherein R₁ is selected from the group consisting of n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methylbutyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-tert-butylphenyl, 4-chlorophenyl, 4-isopropylphenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-n-butoxyphenyl, benzyl, 4-phenylbenzyl, 2-, 3-, or 4-fluorobenzyl, 2-, 3-, 4-chlorobenzyl, 2-, 3-, 4-bromobenzyl, and 4-ethoxybenzyl.

6. A compound of claim 1 wherein R₁ is selected from the group consisting of n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, phenyl, 4-methylphenyl, 4-ethylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-n-butoxyphenyl, benzyl, 4-fluorobenzyl, 4-chlorobenzyl, 4-bromobenzyl, and

4-ethoxybenzyl.

7. A compound of claim 1 wherein R_2 is selected from the group consisting of methyl, 1-cyano-1-phenyl methyl, 2-cyano ethyl, 2-phenylethyl, 2-bromo-2-phenylethyl, 2-bromoethyl, propyl, isopropyl, 3-chloropropyl, 3-bromopropyl, n-butyl, isobutyl, 3-methylbutyl, 1-methylpropyl, tert-butyl, n-pentyl, 3-methylbutyl, n-hexyl, n-heptyl, n-octyl, n-hexadecyl, n-octadecyl, 2-propenyl, 2-propynyl, 3-butenyl, 4-pentenyl, 3-butenynyl, 4-pentenynyl, cyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-cyclohexylbutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminopropyl, phenylaminomethyl, phenyl, 4-methylphenyl, 4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-nitrophenyl, 4-ethoxyphenyl, benzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, and 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 4-ethoxybenzyl, 4-nitrobenzyl, methylcarbonyl, 1-methylcarbonyl methyl, 2-phenylcarbonyl ethyl, isopropylcarbonyl, methoxycarbonyl, ethoxycarbonyl, 1,1-ethoxycarbonyl methyl, 2,2-ethoxycarbonyl ethyl, 1,2-ethoxycarbonyl ethyl, 2-methoxycarbonyl propyl, 3-methoxycarbonyl propyl, 1-ethoxycarbonyl methyl, 1-ethoxycarbonyl ethyl, phenylcarbonyl, phenylcarbonyl methyl, pyridylcarbonyl methyl, pyridylmethyl, pyridylethyl, quinolinylmethyl, pyrrolyl methyl, indolyl methyl, thienyl, thiazolyl, thienylmethyl, thienylethyl, piperdiny methyl, piperaziny methyl, morpholino methyl, morpholino ethyl, morpholino propyl, thiomorpholino methyl, thiomorpholino propyl, 4-methoxybenzenesulfonyl methyl, 3-(4-methoxybenzenesulfonyl)amino propyl, 3-hydroxy, amino, 3-phenoxy propyl, 2-phenyl ethyloxy, (4-butoxybenzenesulfonyl)methyl, methyl-3-(1,5,5-trimethylhydantoin), methyl-3-(1-butyl-5,5-dimethylhydantoin), (4-methoxybenzenesulfonyl)methyl, (4-chlorobenzenesulfonyl)-methyl, (4-bromobenzenesulfonyl)methyl, (n-butylsulfonyl)methyl, (n-octylsulfonyl)-methyl, 3-(4-methoxybenzenesulfonyl)propyl, (4-methylbenzenesulfonyl)methyl, (benzenesulfonyl)methyl, methyl-3-(1-methylhydantoin), methyl-3-(1-butylhydantoin) and methyl-3-(5,5-dimethylhydantoin).

8. A compound of claim 1 wherein R_2 is selected from the group consisting of (4-methoxybenzenesulfonyl)methyl, (4-chlorobenzenesulfonyl)-methyl, (4-bromobenzenesulfonyl)methyl, (n-butylsulfonyl)methyl, (n-octylsulfonyl)-methyl,

3-(4-methoxybenzenesulfonyl)propyl, (4-methylbenzenesulfonyl)methyl, (benzenesulfonyl)methyl, methyl-3-(1-methylhydantoin), methyl-3-(1-butylhydantoin) and methyl-3-(5,5-dimethylhydantoin).

- 5 9. A compound of claim 1 which is
 - (1) N-hydroxy 2-[(4-methoxybenzenesulfonyl) methyl]-3-phenyl-propionamide,
 - (2) N-hydroxy 2-[(benzenesulfonyl)methyl]-3-phenyl-propionamide,
 - (3) N-hydroxy 2-[(benzenesulfonyl)methyl]-propionamide,
 - (4) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-
 - 10 methoxybenzenesulfonyl)-propionamide,
 - (5) N-hydroxy-2-[(4-chlorobenzenesulfonyl)methyl]-3-(4-chlorobenzenesulfonyl)-propionamide,
 - (6) N-hydroxy-2-[(4-bromobenzenesulfonyl)methyl]-3-(4-bromobenzenesulfonyl)-propionamide,
 - 15 (7) N-hydroxy-2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionamide,
 - (8) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(n-octylsulfonyl)-propionamide,
 - (9) N-hydroxy-2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-propionamide,
 - (10) N-hydroxy-2-[(benzenesulfonyl)methyl]-3-(benzenesulfonyl)-propionamide,
 - 20 (11) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide,
 - (12) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - (13) N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - 25 (14) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
 - (15) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - 30 (16) N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - (17) (+)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - (18) (-)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
 - 35 (19) (+)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-

- methoxybenzenesulfonyl)-propionamide,
- (20) (-)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (21) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- (22) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- (23) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (24) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (25) (+)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide, or
- (26) (-)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.
10. A compound of claim 1 which is
- (1) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (2) N-hydroxy-2-[(4-chlorobenzenesulfonyl)methyl]-3-(4-chlorobenzenesulfonyl)-propionamide,
- (3) N-hydroxy-2-[(4-bromobenzenesulfonyl)methyl]-3-(4-bromobenzenesulfonyl)-propionamide,
- (4) N-hydroxy-2-[(n-butylsulfonyl)methyl]-3-(n-butylsulfonyl)-propionamide,
- (5) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(n-octylsulfonyl)-propionamide,
- (6) N-hydroxy-2-[(4-methylbenzenesulfonyl)methyl]-3-(4-methylbenzenesulfonyl)-propionamide,
- (7) N-hydroxy-2-[(benzenesulfonyl)methyl]-3-(benzenesulfonyl)-propionamide
- (8) N-hydroxy-2-[(4-methoxybenzenesulfonyl)methyl]-5-(4-methoxybenzenesulfonyl)-pentanamide,
- (9) N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (10) N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (11) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,

- (12) N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (13) N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.
- 5 (14) (+)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (15) (-)-N-hydroxy-2-[(n-octylsulfonyl)methyl]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (16) (+)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- 10 (17) (-)-N-hydroxy-2-[methyl-3-(1-methylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (18) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- 15 (19) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-butoxybenzenesulfonyl)-propionamide,
- (20) (+)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- (21) (-)-N-hydroxy-2-[methyl-3-(1-butylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide,
- 20 (22) (+)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide, or
- (23) (-)-N-hydroxy-2-[methyl-3-(5,5-dimethylhydantoin)]-3-(4-methoxybenzenesulfonyl)-propionamide.

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11. A method of inhibiting excess matrix metalloproteinase which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

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12. A method of claim 11 wherein matrix metalloproteinases comprises stromelysin, collagenase, and gelatinase.

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13. A method of treating a human suffering from or susceptible to diseases involving connective tissue degradation which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

14. A method of claim 13 wherein the diseases related to connective tissue degradation are osteoarthritis, rheumatoid arthritis, septic arthritis, and osteopenias such as osteoporosis, tumor metastasis, invasion and growth, periodontitis, gingivitis, corneal epidermal ulceration, or gastric ulceration.

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15. The method of claim 11 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

10 16. The method of claim 13 wherein the effective amount of the compound of claim 1 is administered orally, parenterally, or topically in a pharmaceutical composition.

15 17. The method of claim 11 or 13 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

18. A pharmaceutical composition which comprises an amount of the compound of claim 1 effective to inhibit excess matrix metalloproteinase and a pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/16348

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C317/44 C07D233/72 A61K31/16 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 780 386 A (F. HOFFMANN-LA ROCHE AG ET AL) 25 June 1997 cited in the application see page 1, line 1 - page 2, line 5; page 54, line 43, page 57, line 38; claims 1-4, 19, 21-34 ---	1,5,7, 11-18
A	WO 93 20047 A (BRITISH BIO-TECHNOLOGY LTD) 14 October 1993 cited in the application see page 15, line 3 - page 17, line 20; example 14; claims 1, 15-20 ---	1,11-18
A	EP 0 640 594 A (FUJIREBIO INC) 1 March 1995 see page 3, lines 1-46; page 13, lines 2-14; claims -----	1,11,15, 17,18

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

13 January 1998

Date of mailing of the international search report

03.02.98

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INTERNATIONAL SEARCH REPORT

Int'l application No.

PCT/US 97/16348

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 11-17
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/16348

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 780386 A	25-06-97	AU 7548296 A	31-07-97
		CA 2193178 A	21-06-97
		JP 9249638 A	22-09-97
		NO 965413 A	23-06-97
		PL 317604 A	23-06-97
WO 9320047 A	14-10-93	AT 150452 T	15-04-97
		AU 3899193 A	08-11-93
		DE 69309047 D	24-04-97
		EP 0634998 A	25-01-95
		JP 7505387 T	15-06-95
		US 5525629 A	11-06-96
		ZA 9302501 A	08-11-93
EP 640594 A	01-03-95	JP 7126258 A	16-05-95

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